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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-236,238-253 and 256-287* is/are pending in the application.

4a) Of the above claim(s) *6-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *236,238,239,243-253 and 257-287* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment received 26 June 2006 has been entered in full. Claims 1-5, 237, and 254-256 are canceled. Claims 6-235 and 240-242 remain withdrawn from consideration as being directed to a non-elected invention. Claims 236, 238, 239, 243-253, and 257-287 are under examination.

The fourth supplemental declaration of Dr. Heuser under 37 CFR 1.132 and third supplemental declaration of Dr. Lorincz under 37 CFR 1.132 submitted with the response have been entered. A copy of the third supplemental declaration of Dr. Heuser under 37 CFR 1.132 has also been received.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

As an initial matter, it is noted that Applicant comments upon alleged procedural errors. The record has been reviewed and no errors in procedure have been noted. Therefore, these comments will no longer be addressed further.

35 U.S.C. § 112, First Paragraph, New Matter

Claims 248, 249, 252, and 274-279 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter

rejection. The specification, as originally filed, does not contain support for intravenous, intraluminal, or angioplasty delivery of cells.

Applicant's arguments (pp. 41-51, amendment received 26 June 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant points to p. 45, line 1 to p. 46, line 16 for supporting language. This is not found to be persuasive because intravenous, intraluminal, and angioplasty delivery are described as being useful for genes, proteins, or other genetic material, but not for cells. The specification does not include cells in its discussion of "genetic material." For example, p. 31, lines 11-13 state, "...the genetic material comprises comparable artificially produced genes, or genes harvested from other human beings or animals."

Applicant argues that the prior art teaches angioplasty delivery of cells, and thus the new matter rejection with regard to angioplasty balloon delivery of cells is incorrect. This has been fully considered but is not found to be persuasive because written description support for claimed subject matter must be in the specification as originally filed.

Applicant relies on pp. 20, 21, 46, 45, and 44 of the specification for their assertion that "genetic material" includes cells. This has been fully considered but is not found to be persuasive because these sections do not clearly indicate that "genetic material" includes cells. The specification defines "growth factors" as comprising cells, but does not define "genetic material" as comprising cells. For example, p. 31, lines 11-13, of the specification states "...the genetic material comprises comparable artificially produced genes, or genes harvested from other human beings or animals." Page 32,

lines 8-9 state "genetic material can comprise comparable artificially produced genes or genes removed from another animal or otherwise generated." Page 35, line 4 clearly distinguished between growth factors (defined as encompassing cells) and genetic material: "genetic material plus growth factor(s) are implanted..." Page 35, lines 12-14 states "Genetic material is well conserved in nature. The Drosophila eyeless gene (ey), the mouse small ey gene (pax-6), and the Aniridia gene in humans are all homologous." Page 36, lines 25-26 state "Genes control structure and function. A gene or a bit of genetic material may act as a master control gene..." Clearly, the specification uses "genetic material" as pertaining to nucleic acids such as genes. It is also noted that one skilled in the art would only interpret "assistance of a vector," recited in the same sentence that uses "genetic material," as only applying to nucleic acids (genes or RNA or cDNA, etc.).

Applicant points to Capon v. Eshhar v. Dudas, 03-1480-1481 (CAFC 2005) as controlling precedent that 112 does not require recitation in the specification of features already known by workers in the technological field to which the invention is directed. Applicant urges that the examiner's distinction over Capon regarding products or method steps is inapt. This is not found to be persuasive because the instant fact pattern is still found to be distinct from that in the case law cited by Applicant. Capon v. Eshhar, 76 USPQ2d 1078 (CAFC 2005) concerns whether or not claims to chimeric DNA molecules are adequately described by a generic description. The issue here is not whether or not workers in this technology already knew the features of the cells recited in the claims; rather, the issue is that the instant specification did not set forth

contemplation of a method step wherein cells were administered intravenously, intraluminally, or via angioplasty.

Applicant argues that the examiner's reliance on Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) is inappropriate since it also concerns products and not methods, and thus is contradictory to the examiner's position regarding Capon. This has been fully considered but is not found to be persuasive. The issue in Capon speaks to the relevance of what the skilled artisan already knew about cells. However, there was no question of whether or not the cells were set forth in the specification as part of the invention. Lockwood discusses how a specification can show possession of an invention. In the instant case, it does not appear that the originally filed specification set forth contemplation of the administration of cells intravenously, intraluminally, or via angioplasty balloon as being part of the invention. At best, the case law may be somewhat contradictory, and thus is an issue for the Board of Appeals to determine.

Applicant refers to the supplemental declarations of Drs. Heuser and Lorincz, the fourth supplemental declaration of Dr. Heuser, and the third supplemental declaration of Dr. Lorincz, specifically, point 10 of each. Applicant refers to the second supplemental declarations of Drs. Heuser and Lorincz, paragraphs 6 and 10. The declarations have been reviewed again. It is the opinion of Drs. Heuser and Lorincz that the specification's use of the term "genetic material" includes cells. Such constitutes evidence relevant to the issue. However, the specification, for example at pages 31, 32, 35, and 36, uses the term "genetic material" to describe genes. Furthermore, the art

clearly uses the term "genetic material" to mean nucleic acids, not cells. For example, the textbook definition of genetic material set forth in Glossary of Genetics and Cytogenetics (fourth edition, 1976, Rieger et al., eds., p. 237) is provided in Appendix A. The definition for genetic material is:

> "the carrier of primary → genetic information: single or double-stranded → deoxyribonucleic acid (single in some, double in most bacteriophages, bacteria and higher organisms), or → ribonucleic acid (in RNA-viruses). G. M. must fulfill at least two fundamental functions: 1. serve as a template for its own → replication ("autocatalytic function"), 2. provide a template for the synthesis of other classes of macromolecules (specifically proteins), i.e., supply the structural and regulatory information it contains to the protein-synthesizing machinery of the cell ("heterocatalytic function").

Thus, it is a basic tenet of biology that cells do not constitute genetic material, they contain genetic material. It is noted that citing this reference does not constitute a new grounds of rejection. Rather, it is supporting a rejection of record.

Applicant refers to a definition from Wikipedia and pages from a publication called "The Cell Nucleus" to support their assertion that cells contain genetic information. The examiner agrees completely as this is the crux of the issue. Cells contain genetic material, they do not constitute genetic material. The Wikipedia definition, in fact, clearly supports this point.

Applicant argues that the examiner's indication that the specification defines "growth factors" as a genus comprising cells is fatal to the rejection, since p. 46, line 7 indicates that growth factors are a type of genetic material. This is not found to be persuasive. The issue of whether or not the term "growth factors" includes cells was a difficult issue, since the specification contained contradictory statements. For example,

the line referred to by Applicant seems to indicate that cells are separate from growth factors, yet other portions of the specification list cells as belonging to the genus "growth factors." Therefore, the sentence relied upon by Applicant is inherently contradictory.

Applicant urges that the rejection is incorrect when taking the restriction requirement into consideration. Such has been considered but is not found to be persuasive because the elected invention is directed to administration of cells intravenously, intraluminally, or via angioplasty balloon. The specification does not support this concept by an adequate written description.

Applicant concludes that the rejection is improper and hypertechnical in view of the case law and the numerous 132 declarations by Drs. Heuser and Lorincz. This has been fully considered but is not found persuasive for the reasons cited above. Specifically, statements at pp. 31, 32, 35, and 36 of the specification indicate that cells are not considered part of the term "genetic material." Also, the literature clearly indicates that cells *contain* genetic material, but do not *constitute* genetic material (see Appendix A, and the Wikipedia definition submitted by Applicant).

35 U.S.C. § 112, First Paragraph, Enablement

Claims 236, 238, 239, 243-253, and 257-287 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention. The basis of this rejection is of record, but is re-printed here as per Applicant's request.

The claims require formation of a "new" artery. Applicant has defined a new artery as an organ comprising two or more kinds of tissues joined into one structure that has a certain task in the circulatory system. In Applicant's remarks section of the amendment received 17 February 2004, Applicant appears to imply that the "new artery" recited in the claims must be formed *de novo*, and not merely repair, growth or re-direction of an existing artery. See the discussion regarding fusion versus formation of new cells.

The courts have determined several factors to be considered in making a determination of whether or not undue experimentation would have been required of the skilled artisan to make and use the claimed invention (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). These are:

1) quantity of experimentation required,

2) amount of direction/guidance presented in the specification,

3) presence or absence of working examples,

4) nature of the invention,

5) state of the prior art,

6) level of skill of those in the art,

7) predictability, and

8) breadth of the claims.

1) In the instant case, the quantity of experimentation required would be very large. Applicant's attention is directed to pp. 1916 to 1918 of Strauer (of record, 2002, Circulation 106:1913-1918), who review the crucial questions that had to be addressed while designing and realizing their trial of administering stem cells to human patients to repair damaged heart tissue. These included decisions regarding what cell population to use, what delivery method to use, and when cells should be transplanted. As can be seen from pp. 1916-1918, these were not simple or routine matters and involved great quantities of experimentation. In fact, one can see that the determinations of these details involved the act of invention.

2) The specification provides no guidance along the lines of the details worked out by Strauer. The specification broadly asserts that the administration of cells can achieve diverse effects, including growth of any "hard" tissue or "soft" tissue (p. 20), formation of entire new organs (p. 32) or portions of organs (p. 46), restoration of function in any organ (p. 47), formation of auxiliary organs (p. 49), correction of necrosis (p. 49), replacement of missing limbs or body parts (p. 50), treatment of inflammation (p. 50), correction of musculoskeletal injuries or deficiencies (p. 50), formation of hybrid organs (p. 50), etc. No guidance or details are provided as to *how* to achieve these remarkable effects, most of which have never been achieved in this art to this day. The courts have stated that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997). The courts have also stated that "[t]ossing out the mere germ of an idea does

not constitute an enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech Inc. v. Novo Nordisk A/S, *supra*).

3) The specification contains only prophetic examples. In fact, none of the prophetic examples are directed to administration of cells to grow a new artery, thus repairing a dead or damaged portion of a heart. Therefore, there are no examples, working or prophetic, directed to the elected invention.

4) The nature of the invention is highly complex, as evidenced by all of the publications of record, including Strauer. All inventions involving administration of active agents of any kind to a patient to achieve a physiological reaction are complex.

5) The state of the art does not support the specification's (and claims') assertion that a new artery can be grown. None of the numerous post-filing date publications put on the record by Applicant to support enablement of the claimed invention report the *de novo* growth of an artery as defined by Applicant, including Strauer.

6) The level of skill in the art is admittedly high.

7) The invention is unpredictable, as it involves administering active agents to a living patient to achieve a physiological response. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), most chemical reactions and physiological activity involve unpredictable factors. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

8) The breadth of the claims is quite large. The elected invention is directed to a method of administering any type of cell to an undefined area of a human body to grow new cardiac muscle and a new artery (of any type or location) to achieve growth of a new portion of a pre-existing heart.

Due to the large quantity of experimentation necessary to determine how to effectively administer cells to achieve *de novo* formation of cardiac muscle and an artery and thereby grow a new portion of a pre-existing heart, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the effects of an agent on a physiological response, and the breadth of the claims which fail to recite limitations regarding cell type or dosage or site of delivery, etc., undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Additionally, claims 248, 249, and 274-277 are directed to a method of administering cells to a human patient via *intravenous* or *intraluminal* injection to form new cardiac muscle and a new artery and cause growth of a new portion of a pre-existing heart (cl. 248, 249) and repair of dead/damaged portion of said heart (cl. 274-277). Such raises an additional enablement issue for the following reasons. "Intravenous" is a term of art meaning administration into a vein. By definition, a vein is a blood vessel that leads toward the heart. "Intraluminal" is a term of art meaning administration into a "lumen" or cavity, such as the abdominal space or a blood vessel. It is noted that injection into the myocardium is an example of intramuscular

administration, not intraluminal administration. Intraluminal administration into a heart is when a substance is injected directly inside a chamber of the heart. The specification provides no detailed definitions of "intravenous" or "intraluminal" and thus the common, art-accepted definitions provided above are used herein to interpret the claims.

Again considering the guidelines set forth in In re Wands, *supra*, in the instant case, the quantity of experimentation required would be very large. The claims require administration of cells by intravenous or intraluminal injection to repair a dead or damaged portion of a heart. Administration of cells at a site distant to the site at which the cells are intended to adhere and grow had not been achieved in this art at the time of the invention. A great amount of experimentation would be required to determine how to administer the cells other than at the site of heart death/damage, cause the cells to travel to the site of heart death/damage, and then cause the cells to adhere such that repair of the dead/damaged heart portion could be achieved.

The amount of direction/guidance presented by the specification regarding these types of delivery is minimal. The words "intravenous" and "intraluminal" are used at p. 45 of the specification, and are restricted to the administration of VEGF **proteins**, not stem cells. The specification is silent with respect to overcoming the expected obstacles of targeting stem cells that are administered intravenously or intraluminally to the dead/damaged portion of the heart where they can adhere and exert their repairing effects. Thus, the skilled artisan is left with an invitation to experiment to determine how to administer cells intravenously or intraluminally as required by the claims.

There are no working examples directed to administering stem cells to dead or damaged portions of a heart. Although the specification contains prophetic statements that stems cells can be administered to a dead or damaged portion of a heart to repair the heart, no actual experiments or data were disclosed.

The nature of the invention is extremely complex. Evidence of this can be found in the relevant art. As stated in Murry et al. (of record, 1996, J. Clin. Invest. 98:2512-2523), "the goal of limiting myocardial injury has been difficult to achieve clinically, because ischemic myocardium dies quite rapidly and most patients wait more than 3 h after coronary occlusion before seeking medical attention" (p. 2512, Introduction).

The state of the prior art indicates that only localized injection of cells can successfully treat damaged myocardium. See Murry et al. (*supra*), Klug et al. (1996, J. Clin. Invest. 98:216-224), Oakley et al. (2001, Ann. Thorac. Surg. 71:1724-1733), Chiu et al. (1995, Ann. Thorac. Surg. 60:12-8), Yoon et al. (1995, Tex. Heart Inst. J. 22:119-125), Koh et al. (1993, J. Clin. Invest. 92:1548-1554), Van Meter et al. (1995, J. Thorac. Cardiovasc. Surg. 110:1442-1448), and Koh et al. (1995, J. Clin. Invest. 95:114-121). All used intramuscular injection of cells directly into the myocardium.

The level of skill of those in the art is admittedly high.

The art is considered unpredictable, since it could not be predicted if cells administered intravenously or intraluminally would reach the site of heart death/damage. Also, the courts have acknowledged that inventions utilizing biological systems are unpredictable. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable

factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). In the instant case, not even one single embodiment has been exemplified for this unpredictable system.

The claims are considered broad, since no details of the administration method other than "intravenous" or "intraluminal" are recited. For example, no dosages or targeting molecules are recited. No specific types of cells that would be expected to travel to the desired site are recited.

Due to the large quantity of experimentation necessary to determine how to administer cells intravenously or intraluminally to achieve growth of a new portion of a distant pre-existing heart, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of targeting cells to a distant site, and the breadth of the claims, it is determined that undue experimentation would have been required of the skilled artisan to practice the claimed methods.

Applicant's arguments (pp. 51-104, amendment received 26 June 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant states that they understand the rejection to be based upon a lack of enablement for the administration of cells by intravenous and intraluminal techniques to

a human patient to grow new cardiac muscle and a new artery and thus grow a new portion of a pre-existing heart. Applicant argues that the examiner incorrectly interpreted the claims as requiring repair of dead/damaged heart tissue. Applicant states that the USPTO is obligated to apply uniform standards of examination to maintain prosecution integrity and thereby ensure that administrative due process is accorded to all applicants. Applicant states that the examiner has applied inconsistent standards in concurrent examinations of the instant application and that of recently granted U.S. Patent 6,844,312 (Weiss). Applicant compares the instant application with the Weiss patent. Applicant's arguments have been fully considered but are not found to be persuasive. First, claims 274-277 now require repair of dead/damaged heart tissue. Next, each application is examined on its own merits, and the actions taken in the Weiss patent have no bearing on the instant procedure. Also, none of the claims in Weiss recite intravenous or intraluminal injection of cells. Furthermore, the therapeutic result required by the claims is different, the filing dates are different, the state of the art for each invention is different, and the disclosures are different. There has been no gross inconsistency on the part of the examiner.

Applicant reviews the legal standard for enablement with which the examiner takes no issue.

Applicant argues that the questioned intravenous and intraluminal administration techniques were well established in the medical arts prior to Applicant's invention. Applicant argues that cells, including stem cells, were well known and characterized prior to the invention. Applicant points to the existence of stem cell banks. Applicant

argues that Dr. Elia's contribution to the medical arts was that an artery can be grown and a human heart repaired through use of a new combination of old administration techniques and old cellular materials. Applicant urges that one skilled in the medical arts would be enabled to make and use the claimed invention without resorting to more than routine experimentation based on the instant disclosure. Applicant also points to the expert opinions of Drs. Heuser and Lorincz as confirming this statement. This has been fully considered but is not found to be persuasive. The invention defined in claims 16, 17, 30, 31, and 47-52 is directed to a method of repairing a dead or damaged portion of a pre-existing heart comprising placing cells at a selected area of a human patient; and forming a new artery, thereby causing said dead or damaged portion of said hear to be repaired; wherein the cells are administered by intravenous or intraluminal injection. These claims thus require that the cells be administered at a location other than the site of the injury (e.g., the myocardium). The original rejection carefully considered all of the factors relevant to the question of enablement and whether or not undue experimentation would have been required of the skilled artisan to make and use the claimed invention. Please see pp. 4-8 of the non-final office action mailed 28 November 2003. Regarding the contributions of Dr. Elia to the art, such appears to be more relevant to the issue of novelty and obviousness than to the issue of enablement. The Heuser and Lorincz declarations will be addressed in turn.

Applicant states that the only evidence relied upon by the examiner is the Strauer et al. and Deb et al. publications. Applicant argues that the high-pressure, angioplasty balloon injection technique of Strauer was not a "specialized form of intraluminal

delivery" as characterized be the examiner. Applicant argues that, whether or not the technique of Strauer was "specialized," it is allegedly evident that many other techniques may be used to perform the claimed method. Applicant refers to Wollert et al. (2004, Lancet 364:141-148) as achieving the required results using only a simple infusion of cells rather than a high pressure injection of cells. Applicant urges that, while the examiner has made an unsupported assertion to the contrary (in the advisory action at pp. 17-18), Wollert does not report high pressure injection and still achieves heart repair. Applicant concludes that the disclosure's failure to mention high pressure is of no moment because Wollert shows that lower pressure is operative. This has been fully considered but is not found to be persuasive. It is important not to lose sight of the fact that the claims recite intraluminal injection. This encompasses injection of cells into any lumen, which includes veins, arteries, intestines, intraperitoneal cavity, etc. Both Strauer and Wollert are limited to intraluminal injection into the infarct-related coronary artery, right at the site of the injured tissue. Thus, Strauer and Wollert do not constitute evidence to support enablement commensurate in scope with the claims. Regarding the high pressure injection question, Wollert discloses:

> "6-8 h after bone-marrow harvest, the final preparation of bone-marrow cells was infused into the infarct-related artery via the central lumen of an over-the-wire balloon catheter (Concerto, Occam International Eindhoven, Netherlands). To allow bone-marrow cells maximum contact time with the microcirculation of the infarct-related artery, the balloon was inflated inside the stent to transiently interrupt antegrade blood flow during infusions. The entire bone-marrow cell preparation was infused during four to five coronary occlusions, each lasting 2.5-4 min. Between occlusions, the coronary artery was reperfused for 3 min." (third page of the electronic form of the document attached to the response to the final action, received 30 July 2004)

It is respectfully submitted that, while Wollert does not actually use the words "high-pressure," that the method was actually high-pressure to achieve "interrupt antegrade blood flow" for "2.5-4 min." during "four to five coronary occlusions." High-pressure injection is necessarily achieved by a balloon catheter. The Wollert method is remarkably similar to the method used by Strauer:

> "Five to nine days after the onset of acute infarction, ells were directly transplanted into the infracted zone (Figure 1). This was accomplished with the use of a balloon catheter, which was placed within the infarct-related artery. **After exact positioning of the balloon at the site of the former infarct-vessel occlusion, percutaneous transluminal coronary angioplasty (PTCA) was performed 6 to 7 times for 2 to 4 minutes each.** During this time, intracoronary cell transplantation via the balloon catheter was performed, using 6 to 7 high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to $4X10^6$ mononuclear cells. **PTCA thoroughly prevented the backflow of cells**..." (p. 1914, emphasis added).

In conclusion, both Strauer and Wollert use remarkably similar techniques to implant cells at the site of the infarct-related injury. Such does not constitute evidence commensurate in scope with the rejected claims, which merely recite intravenous or intraluminal injection of cells. Finally, It is noted that the instant specification only states that cells ("multifactorial and non-specific cells" or "stem cells" or "germinal cells") can be used to grow an organ or repair/replace dead or damaged heart tissue. No specific guidance regarding *how* to obtain appropriate cells, *how* to administer them, *how* to monitor success, etc. are provided. The Strauer and Wollert references provide evidence of the large quantity of experimentation that was still required after Applicant's claimed priority date in order to achieve some beneficial result.

Applicant argues that Strauer 2002 did not state that other administration techniques, such as intramuscular or intravenous, were inoperative but instead considered such techniques not as efficient as his technique. Applicant refers to Strauer 2003 as supporting intravenous administration as "easiest." Applicant refers to Phase I trials of Osiris as supporting enablement of intravenous administration of cells for heart repair. This has been fully considered but is not found to be persuasive. Strauer 2003 does not report any results after using intravenous administration, and cannot be interpreted as indicating that intravenous administration is easiest. Furthermore, the diagram in Strauer 2003 shows intravenous administration into a vein on the surface of the heart, not at a site distant from the heart. Osiris also does not report efficacy results. No experimental details are provided for either Strauer 2003 or Osiris, so it is impossible to determine if the evidence is commensurate in scope with the claims or if different methodologies or pharmaceuticals were used.

Applicant argues that Strauer 2002 does not provide a side-by-side comparison, and thus the examiner's comments are speculative. Applicant refers to cf. Hormone Research Foundation v. Genentech. Inc., 904 F.2d 1558, 15 USPQ 2d 1039 (Fed.Cir.1990). Applicant argues that all an applicant is required to do is to provide a disclosure that one skilled in the art can understand and then follow to make and use the invention. Applicant concludes that any failure to disclose a later developed technique has no bearing upon enablement. This has been fully considered but is not found to be persuasive. Strauer 2002 clearly indicates that intravenous administration is not expected to provide beneficial results. See p. 1917, left column, second

paragraph. The issue is not whether or not Applicant is required to foresee improvements, but whether or not sufficient guidance is present in the specification as originally filed to enable one skilled in the art to make and use the claimed invention without resorting to undue experimentation. The fact that the references published well after the claimed priority date reported the necessary development of techniques and materials to successfully achieve repair of damaged myocardium, wherein these techniques and materials are not disclosed in the instant specification, evidences the significant amounts of further experimentation that was required to achieve growth of a new portion of a pre-existing heart by administration of cells. Such development of new techniques and materials constitutes part of the act of invention. Regarding Hormone Research Foundation v. Genentech. Inc., 904 F.2d 1558, 15 USPQ 2d 1039 (Fed.Cir.1990), the court found that "[t]he '833 specification itself discloses that Dr. Li's claimed method had produced the material depicted in Figure 1 of the '833 patent and that such a material exhibited lactogenic activity. Evidence tending to support this assertion can be found in several of the journal articles of record." Thus, the disclosure at issue in Hormone Research Foundation v. Genentech. Inc. disclosed considerably more detailed disclosure compared to the instant application, included working examples and figures, and was supported by other published evidence. The instant fact pattern is more akin to that in Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997). The court stated that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". The court also stated that "[t]ossing out the mere germ of an

idea does not constitute an enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech Inc. v. Novo Nordisk A/S, supra).

Applicant again refers to the Weiss patent. The Weiss patent is not relevant to the issues of the instant application, since each application is examined on its own merits.

Applicant argues that the examiner raised generalized concerns regarding properties and handling of cells in the prosecution of the instant application. Applicant characterizes these concerns as opinion rather than factual evidence. Applicant argues that properties of cellular materials were well established prior to the filing date and refers to several documents in support of such. Applicant argues that official notice can be taken that stem cell culture techniques have been known and used decades prior to Applicant's filing date, and that any skilled person in the medical arts would be familiar with the properties and stem cell handling techniques at issue. This has been fully considered but is not found to be persuasive. The rejection was based on evidence (see publications cited at p. 7 of the non-final office action mailed 28 November 2003, as well as Strauer and Wollert) and sound scientific reasoning, not mere opinion. Proper legal analysis of all of the Wands factors was set forth on the record (non-final office action mailed 28 November 2003). The first of four pieces of evidence referred to by Applicant, the Caplan abstract, does not overcome the rejection. Caplan discusses the differentiation of cells *in vitro* into specialized cells for localized administration, and the use of cells as gene therapy vectors. Such is not relevant to the issue at hand. The

second piece of evidence, Merck has to do with cancer and does not appear to be relevant. The third piece of evidence, NIH report, lists results of a web search for "nonspecific growth factor" and also appears to be irrelevant to the issue at hand. The last piece of evidence, Exhibit III in the after final amendment, reviews traditional use of cells for cancers and immunotherapy, and newer uses as gene therapy vehicles. None of these treatments involve the systemic administration of cells to repair a distant organ.

Applicant argues that administration of cells is old in the art. This point is conceded.

Applicant argues that the examiner's statement regarding Deb et al., wherein it was acknowledged that cells administered intravenously could migrate to the art, should end all speculation regarding enablement of the claimed invention. This has been fully considered but is not found to be persuasive because Deb et al. do not demonstrate that cells can migrate to the heart in sufficient quantities to repair any defects. Deb discloses that only $0.23 \pm 0.06\%$ of the cardiomyocytes were from the transplanted cells. Such numbers of cells are greatly insufficient to achieve the effects required by the claims. As evidence of this, Strauer 2002 administered 6 to 7 fractional high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to 4×10^6 mononuclear cells directly to the infarct site in order to achieve their effects. In fact, Strauer 2002 specifically points to shortcomings of intravenous administration at p. 1917. The evidence as a whole indicates that intravenous administration of cells to repair a dead or damaged portion of a heart has not yet been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and

preventing them from re-migrating away from the site. As this problem has not yet been solved in the literature, and no suggestions for solving the problem are suggested in the specification as originally filed, undue experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result.

Applicant argues that Deb et al. specifically suggest that human bone marrow can be used as a source of extracardiac progenitor cells capable of de novo cardiomyocyte formation at p. 2 of the conclusion section. This has been fully considered but is not found to be persuasive because Deb et al. do not suggest administration of bone marrow cells intravenously to achieve cardiomyocyte formation. Rather, they suggest that bone marrow can be used as a *source*.

Applicant argues that Strauer 2002 and Wollert also provide evidence that cells can migrate to the infarct zone. This has been fully considered but is not found to be persuasive. Strauer 2002 and Wollert administered cells at the heart. Such is not commensurate in scope with "intravenous" or "intraluminal" administration, which reads on administration at sites far distant from the heart (e.g., a vein in the arm, the lumen of the intestinal tract).

Applicant argues that the lack of teachings regarding dosages in Deb et al. is irrelevant since Deb et al. were not addressing repair of damaged heart tissue. Applicant argues that it would have been routine to administer cells multiple times to achieve the desired result. Applicant points to Strauer 2002 as not teaching that intravenous administration is inoperative. Applicant points to Strauer as using seven infusions, and p. 45 of the specification as suggesting sequential administrations of

growth factors. This has been fully considered but is not found to be persuasive. Deb et al. Page 45, lines 26-27 of the specification read as follows :

"It may be necessary to provide gene(s) or growth factor(s) sequentially. For instance, one or more blood vessels are grown by inserting an appropriate gene or other genetic material into a selected area. Second, an appropriate gene or other genetic material is inserted in the selected area to grow a bone or other organ." Clearly, this section of the specification is directed to sequential administrations to achieve *different* effects. There is no guidance regarding multiple administrations to achieve one effect. Also, there is no guidance in the specification or the prior art regarding how many intravenous or intraluminal administrations of cells are needed to achieve growth of a new portion of a pre-existing heart. Deb et al., Strauer 2002, and Wollert cannot be relied upon to provide the missing guidance, since they were published after the instant filing date.

Applicant argues Applicant argues that coupling Deb and Strauer is inappropriate since Deb is not concerned with growth of a new portion of a pre-existing heart. Applicant urges that the examiners' position is without evidence. Applicant argues that Strauer indicates that intravenous administration is operative. Applicant concludes that it was well within the skill of the art to select an appropriate number of cells and number of infusions. This has been fully considered but is not found to be persuasive. Since Applicant has relied on both Deb and Strauer, it was not inappropriate to point out deficiencies in the references. Strauer 2002 clearly teaches away from intravenous

administration. Finally, the concept of multiple administrations for a single effect does not appear to be disclosed in this specification.

Applicant argues that "remigration" is not an insurmountable problem because Wollert succeeded. Applicant argues that the examiner has fabricated problems and that the invention need not be optimized in order to be patentable. This has been fully considered but is not found to be persuasive. Again, it is important to remember that Wollert is limited to intraluminal injection into the infarct-related coronary artery, right at the site of the injured tissue. Thus, Wollert does not constitute evidence to support enablement commensurate in scope with the claims, which encompass intravenous or intraluminal administration at any vein or lumen. Furthermore, the specification does not provide guidance along the lines of Wollert's use of large quantities of cells and multiple administration passages to overcome re-migration problems identified by others in this art.

Applicant provides comments regarding the multiple declarations by Drs. Heuser and Lorincz. Applicant urges that Drs. Heuser and Lorincz are eminently qualified, and that the examiner has improperly dismissed the evidence of the declarations. Applicant argues that enablement is a question of fact. Applicant argues that the evidence indicates that only routine experimentation would have been required of the skilled artisan to make and use the claimed invention. This has been fully considered but is not found to be persuasive. There is no question that Drs. Heuser and Lorincz are distinguished doctors. However, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought

to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). The nature of the fact sought t be established is whether or not more than routine experimentation would have been required to practice the claimed invention in its full scope. This issue has been extensively addressed on the record with reference to the Wands factors and the publications of record. It is maintained that more than routine experimentation would have been required. The strength of opposing evidence has also been addressed extensively on the record. The post-filing date publications are filled with specific guidance necessary to achieve the desired results. This specific guidance is absent in the instant specification. Finally, the claims are incredibly broad, reciting general intravenous or intraluminal administration. The post-filing date art that achieves any growth of new portions of pre-existing hearts used specific administration methods that are not specifically pointed to in the specification. Regarding the interest of the experts in the outcome of the case, there is no evidence that there is any such interest. Finally, there is a question of the presence or absence of factual support for the expert's opinion. Mostly, the experts relied upon the specification itself, which has been separately addressed. However, some publications were also referred to. These have been addressed on the record. Thus, the declarations have been fully considered and a finding that the rejection should be maintained is proper. As an aside, it is

respectfully submitted that Applicant is mistaken in their statement that enablement is a question of fact. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. Thus, while no weight is given to the experts' opinion regarding the ultimate legal conclusion of enablement, the underlying basis for the legal conclusion has been considered.

Applicant next discusses the Wands factors. Again, the Wands factors have been extensively reviewed on the record. Applicant's arguments are duplicative of arguments already made and addressed on the record. In view of consideration of the preponderance of the totality of the evidence, the rejection is maintained.

35 U.S.C. § 112, Second Paragraph

Claim 245 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments (pp. 36-41, amendment received 26 June 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the rejection is inconsistent with the decision on a parent patent, 5,759,033. This has been fully considered but is not found to be persuasive. The prior examiner's position is not binding. Furthermore, in general, it is not the policy of the USPTO to perpetuate errors. When issues are first identified, they must be raised.

Applicant refers to the Philips decision. The same argument appeared in the response received 21 November 2005 and has already been addressed in the office action mailed 16 February 2006.

Applicant refers to the declarations of Drs. Heuser and Lorincz. These have also already been addressed.

Applicant refers to Exhibits as additional evidence in support of their position. While these references do, in fact, refer to proteins as multifactorial, they define the exact, specific effects the proteins have. Therefore, the entire phrase "multifactorial and non-specific" as it relates to cells, is still not defined.

Applicant points to Strauer 2005, Caplan 1991, and Caplan 2001 as using the term "multifactorial" to describe cells. Strauer 2005 does not use the term multifactorial to describe cells. Rather, Strauer 2005 uses "four mechanisms" to describe "regenerative potential" and not cells *per se.* Also, Strauer 2005 only discusses bone marrow cells, which are already indicated by the specification as exemplary of "multifactorial and non-specific" cells, and thus does not provide evidence regarding what cells other than stem cells and germinal cells can be termed "multifactorial and non-specific." Regarding Caplan 1991, the examiner is at a loss as to how Applicant can conclude that the publication uses the term "multifactorial and non-specific" to describe MSCs from the quoted passages. Caplan 2001 uses the term "multifactorial" to describe the differentiation pathway, a process, and thus supports the examiner's position.

Applicant refers to Exhibit G. This describes a drug as a non-specific growth factor for megakaryocytes. This also does not resolve the issue since it does not address the question of what "mutlifactorial and non-specific" means in terms of cells.

Applicant argues that the phrase "multifactorial and non-specific" has been used to describe or characterize the potentialities of stem, germinal, and pluripotent cells. This has been fully considered but is not found to be persuasive. While the phrase "multifactorial and non-specific cells" appears in the specification, there is no clear definition of what cell types are encompassed by the term, for the reasons of record. Page 37 of the specification states, "Multifactorial and nonspecific cells (**such as** stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated" (emphasis added). The use of "such as" clearly implies that the term "multifactorial and non-specific cells" is intended to encompass cells other than stem cells and germinal cells. However, neither the specification nor the art disclose what these other cells are. In the absence of this information, the skilled artisan cannot determine the metes and bounds of the claims at issue.

In conclusion, the term "multifactorial and non-specific cells," recited in claim 245, is not defined unambiguously in the art or in the specification, for the reasons set forth above. Therefore, the skilled artisan cannot determine the metes and bounds of the claimed invention, and the rejection is proper.

Double Patenting

Claims 286 and 287 of this application conflict with the claims of Application No. 09/794,456. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 286 and 287 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/794,456. Although the conflicting claims are not identical, they are

not patentably distinct from each other because the instant and c-pending claims are generally directed to methods of repairing dead or damaged portions of a pre-existing heart by administering stem cells and forming a new artery.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER